Editorial

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IL28B testing in a rapidly changing world: Still relevant?

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In 2009, a now seminal genome wide association study led to the discovery of a nucleotide polymorphism, rs12979860, upstream of the interleukin 28B (*IL28B*) gene. The CC *IL28B* genotype was associated with an over twofold improvement in response to treatment with pegylated interferon and ribavirin (PR) in patients with genotype 1 chronic hepatitis C virus (HCV) infection [1]. In an intention-to-treat analysis evaluating on-treatment virologic response and sustained virologic response (SVR) in a large cohort of genotype 1 HCV infected patients, the CC *IL28B* genotype was associated with an improved SVR in Caucasians of 69% as compared to 33% for the CT and 27% for the TT genotypes. These findings were similar across other ethnic groups. The CC *IL28B* genotype was the strongest pretreatment predictor of SVR. Rapid virologic response (RVR) was a strong predictor of SVR regardless of *IL28B* genotype, and in non-RVR patients, the CC *IL28B* genotype was associated with a higher rate of SVR [2]. Given the lack of alternative therapies, the multiple side effects of dual therapy, and the prolonged course of treatment with overall low rates of cure, *IL28B* testing held promise as a prime example of applying pharmacogenomics to the planning of antiviral therapy. However, the discovery came at a time when HCV treatment was undergoing significant evolution with the development of direct acting antiviral (DAA) agents.

In 2011, the first generation HCV protease inhibitors, telaprevir, and boceprevir, were approved in combination with PR for genotype 1 HCV infection. With a nearly twofold increase in SVR compared to PR alone, the utility of *IL28B* genotyping could be called into question. Would the improved outcome for all comers accompanying telaprevir and boceprevir effectively nullify the predictive value of *IL28B* genotype? Or, could *IL28B* genotyping be used to determine which patients should succeed equally well receiving standard dual therapy versus triple therapy, especially given the cost of the DAAs? Could *IL28B* genotyping identify those patients who could receive an abbreviated course of therapy or could this question be answered with on-treatment virologic milestones alone? While *IL28B* genotyping was not available during the prospective randomized trials for the initial DAAs, retrospective analysis of those patients who consented for genetic testing has been performed.

In a retrospective analysis of those patients who consented to genetic testing in two large boceprevir trials for treatment naïve (SPRINT-2 [3]) and treatment experienced (RESPOND-2 [4]) patients, the main role for *IL28B* genotyping was in the prediction of those patients who could receive a shorter duration of therapy in the response guided therapy groups. In the SPRINT-2 trial, in which patients were randomized to 4 weeks of PR lead-in followed by 44 weeks of boceprevir and PR, a response guided therapy group, in which all patients received a 4 week PR lead-in and then boceprevir and PR for an additional 24 weeks, with an additional 20 weeks of PR if the viral load was detectable between weeks 8 and 24, or 48 weeks of PR alone, SVR rates for the favorable *IL28B* CC patients were high regardless of treatment arm (78% for PR alone, 82% for boceprevir response guided therapy group, and 80% for boceprevir/PR 48 week group). *IL28B* genotype was independently associated with the outcome of boceprevir based therapy. When interferon responsiveness, defined as a $\geqslant 1 \log_{10}$ decline in HCV viral load at week 4 was added to the multivariable logistic regression model, *IL28B* genotype was no longer a significant predictor of SVR, indicating that on-treatment viral kinetics are the functional equivalent of *IL28B* genotype. Low baseline viral load, absence or cirrhosis, HCV subtype 1b, and lower BMI did remain significant predictors of SVR. For previously treated patients, *IL28B* genotype was not a significant predictor of overall SVR; only a $\geqslant 1 \log_{10}$ decline in week 4 HCV viral load and prior response category, previous relapse versus previous non-response, were significant. Again, more patients in the CC category were eligible for a shortened duration of therapy [5].

There had been more limited data for the role of *IL28B* genotyping in patients receiving telaprevir. *IL28B* in telaprevir treatment naïve patients was evaluated retrospectively in 42% of patients in the ADVANCE [6] study population. Only Caucasians were included in this analysis. Since genotyping was performed in de-identified specimens, no formal statistical analysis was performed and other clinical and demographic data such as viral load and fibrosis stage were not evaluated. Rates of SVR in the telaprevir group were higher than in the PR group among all patients (CC and non-CC). Again, the presence of the *IL28B* CC genotype identified patients who were eligible for a shortened duration of therapy (those that achieved extended RVR (eRVR) as defined by undetectable HCV RNA at weeks 4 and 12). However, as with boceprevir, on-treatment viral kinetics were the

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main predictor of SVR, since SVR rates were excellent in all patients who achieved eRVR regardless of *IL28B* genotype. Ninety one percent of those telaprevir-treated eRVR patients achieved SVR (97% CC, 88% non-CC) with 24 weeks of therapy, whereas only 45% of non-eRVR telaprevir patients had SVR with 48 weeks of therapy. Among non-EVR patients, *IL28B* testing had more utility, as SVR was higher in CC (67%) as compared to non-CC (38%) patients [7]. In a sub analysis of the PROVE2 trial [8] in which non-cirrhotic treatment naïve HCV genotype 1 patients were randomized to 12 weeks of telaprevir and PR, 12 weeks of telaprevir, PR and an additional 12 weeks of PR, 12 weeks of telaprevir and PegIFN alone, or 48 weeks of PR, 100% (12/12) of the genotype CC patients achieved an SVR with only 12 weeks of telaprevir and PR [9], suggesting that patients with *IL28B* CC genotype may be eligible for an even shorter course of therapy than described in the ADVANCE trial.

In their sub analysis of the REALIZE study, Pol *et al*. provide us with the missing piece of the puzzle on the role of *IL28B* testing in the current era of triple therapy. They evaluated the impact of *IL28B* genotype on SVR in telaprevir-treated HCV genotype 1 infected patients who had previously failed treatment with PR, including null responders. In the REALIZE study, 662 patients were randomized to 12 weeks of telaprevir with or without a 4 week PR lead in or placebo, each with PegIFN-α-2a and ribavirin for 48 weeks overall [10]. Eighty percent of the subjects consented to genetic testing and were included in this retrospective analysis. Since the original trial showed no significant difference between the two telaprevir arms, these groups were pooled for this study. SVR rates were higher in patients who received telaprevir *vs*. placebo for all *IL28B* genotypes, CC 79% *vs*. 29%, CT 60% *vs*. 16% and TT 61% *vs*. 13%. SVR rates were similar irrespective of *IL28B* genotype for prior relapsers and prior partial responders. For prior null responders, SVR rates were slightly higher for the *IL28B* CC genotype than for non-CCs. In multivariable modeling, *IL28B* genotype did not significantly affect SVR. Prior response category, did however significantly affect SVR [11]. Thus, from this informative analysis, we can conclude that there is a limited utility for *IL28B* testing in treatment experienced patients being considered for telaprevir therapy, especially those patients who have well defined prior treatment courses.

Taken together, the results of the retrospective analyses of the REALIZE, ADVANCE, SPRINT-2, RESPOND-2, and PROVE2 trials indicate a limited role for *IL28B* genotyping. For treatment naïve patients, the role of genotyping would appear to be limited to encouraging those patients contemplating triple therapy to undertake treatment because they would have a high likelihood of requiring an abbreviated course of therapy. Interestingly, cost effectiveness modeling studies have suggested that for those with the CC genotype, dual PR therapy may be more cost effective [12,13]. This, however, depends on the cost of the DAAs. For treatment experienced patients whose prior treatment courses have been well defined in terms of quantitative HCV reduction, there is no clear role for *IL28B* genotyping, since their interferon responsiveness has already been defined. *IL28B* genotyping may be more helpful in counseling those patients whose prior treatment courses have not been well defined. Overall, though, on-treatment kinetics will still be the most valuable predictor of response in addition to other known clinical variables, such as absence of cirrhosis and pretreatment viral load.

While these analyses are useful in clarifying the role for *IL28B* in triple therapy, as we enter 2013, they are about to again be supplanted by all oral interferon-free DAA regimens. What role will there be for *IL28B* genotyping in the era of interferon-free regimens? This question has been studied prospectively. In the SOUND-C2 study, the efficacy and safety of interferon-free combination regimens of faldaprevir, an NS3/4A protease inhibitor and BI207127, a non-nucleoside NS5B polymerase inhibitor, with or without ribavirin in 362 genotype 1 HCV treatment-naïve patients were evaluated. Of interest, *IL28B* genotype, genotype 1 subtype, and gender were identified as significant baseline predictors of SVR. The difference in response to therapy according to *IL28B* subtype was confined primarily to 1a, since 1b patients did uniformly well [14]. The finding of a predictive value for *IL28B* genotype indirectly suggests the contribution of the host innate immune response even to an IFN-sparing all-DAA regimen. Recently Poordad *et al*., evaluated ABT-450, an NS3 protease inhibitor, boosted with low-dose ritonavir, plus ABT-333, a non-nucleoside NS5B polymerase inhibitor, and ribavirin in genotype 1 HCV infected patients. For previously untreated patients, up to 95% of patients experienced an SVR 12 weeks after the end of treatment, and all previously untreated patients with CT/TT *IL28B* genotypes experienced SVR [15]. It was also recently shown that the combination of ABT-450/ritonavir with ABT-333 and another DAA, ABT-267, led to an SVR 12 weeks after therapy completion in 93% (42/45) of previous null responders despite a high frequency of the non-favorable *IL28B* non-CC genotype [16]. In a study of the nucleotide polymerase inhibitor sofosbuvir and ribavirin, 21/25 previously untreated patients with genotype 1 HCV achieved SVR 24 weeks after therapy. 11/25 patients were genotype CC [17]. Thus, while there may be a role for *IL28B* genotyping in genotype 1a patients for some DAA combinations, emerging data on regimens with very high SVR rates will likely limit *IL28B* testing to difficult-to-treat-patients or to justification of even more simplified regimens in uncomplicated patients. As treatment options for HCV rapidly unfold, so too must our ability to provide predictive tools that enable us to tailor therapy to the individual patient.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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